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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/203,078	12/01/1998	SHUYUAN ZHANG	INRP:081	3754

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STEVEN L. HIGHLANDER
FULBRIGHT & JAWORSKI L.L.P.
600 CONGRESS AVENUE, SUITE 2400
AUSTIN, TX 78701

EXAMINER	
FOLEY, SHANON A	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 11/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/203,078	ZHANG ET AL.	
	Examiner	Art Unit	
	Shanon Foley	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31 and 33-62* is/are pending in the application.

4a) Of the above claim(s) *33-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31 and 38-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/5/4, 7/13/3, 3/27/00*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

In the amendment submitted September 7, 2004, applicant amended claim 48 and cancelled claim 32. Claims 1-31 and 33-62 are pending, claims 33-37 are withdrawn from consideration due to nonelected subject matter and claims 1-31 and 38-62 are under consideration.

Upon review of the file history, it appears that some of the references that have previously been submitted by applicant as exhibits, such as Kuchler and Freshney, are incomplete. For example, the Freshney reference only contains the title page and page 239 and the Kuchler reference available for review contains the title page and pages 91, 99 and 100. Since paragraph 10 of Mr. Gallagher's declaration mentions page 90 of Kuchler, it appears that the electronic conversion of the application by the Office did not scan all of the pages of these references. Applicant is requested to supply a copy of all of the references in exhibits again so that the Office file history is complete. Any inconvenience experienced by applicant is regretted.

Information Disclosure Statement

Since the new electronic scanning system at the Office has been implemented, it cannot be determined from our file records if the IDS's submitted April 5, 2004, July 14, 2003 and March 27, 2000 have been considered. In any case, the IDS's have been presently considered or reconsidered and an initialed, signed copy of each is being forwarded to applicant.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686

F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

In the previous Office action, Pre-grant Publication Patent Application No. US 2002/018723 A1 was applied in a provisional rejection. In response, applicant has supplied a copy of the currently pending claims in the corresponding application no. 09/880,609. Applicant states that the instant claims and the '609 claims are believed to be patentably distinct.

A copy of the '609 claims provided by applicant have been considered. However, claims 30 and 31 of '609 are not considered to be patentably distinct from instant claims 1 and 29 for the reasons previously presented. If claims 30 and 31 of '609 and instant claims 1 and 29 had been filed in the same application, a restriction could not have been drawn between the two sets of claims because the subject matter is not divergent, the process is only able to make the single product claimed and the product claimed can only be made by the single process. Therefore, claims 30 and 31 of '609 and instant claims 1 and 29 are not patentably distinct.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, 8, 9, 13-25, 31, 38, 47, 49 and 51-62 are rejected under 35 U.S.C. 102(b) as being anticipated by Huyghe et al. (Human Gene Therapy. 1995; 6: 1403-1416) in light of Kuchler for reasons of record.

In response to the issue of seeding density in section 1 bridging pages 12-13 of the response, applicant reasons that since the assumed seeding densities of Huyghe et al., provided by Mr. Gallagher's February 13, 2002 declaration, are found to be speculative and unsubstantiated, the Office's position must also speculative and unsubstantiated. Both the Office and applicant appear to agree that Huyghe et al. do not discuss seeding densities. However, the Office does not and has not ventured to speculate or assume seeding densities that cannot be substantiated by Huyghe et al., as applicant has, since the reference does not discuss seeding densities. Applicant has not provided any argument or data sufficient to support the assumptions present in the declaration and the rejection is maintained.

Applicant asserts that Mediatech states that one should use 70% confluent cultures to ensure that they are in log phase. Applicant states that this teaching implies that cultures that are less confluent than 70% cannot be assured of being in log phase.

Applicant's arguments as well as a review of the reference have been fully considered, but are found to be unpersuasive. Mediatech correlates cells that are at least 70% confluent with log phase, see the top of the second column:

"Subculturing is usually performed during the log phase....[c]heck for cultures that appear to be at least 70% confluent."

However, Mediatech does not differentiate cell confluency with the degree of log phase the cells may be in. For instance, Mediatech does not teach whether 70% confluency correlates to early, mid or late log phase. The reference only provides a general teaching that 70% confluency is log phase. Without any guidance provided by Mediatech regarding the percentage of confluency and the stage of log growth, it is maintained that a definite identification of which log phase a cell culture is in based on a percentage of confluency cannot be determined.

Regarding the teachings of Kuchler, applicant states that there is no correlation provided by the Office as to how or why the fibroblast suspension cultures of Kuchler and the 293 cells of Huyghe et al. are connected. However, applicant made the correlation when the reference was supplied to the Office for the general statement regarding typical lag phase and hours. Since the general teaching of Kuchler relied on by applicant as applying to the cells of Huyghe et al. is relevant, it is determined that all of the general teachings of Kuchler are relevant.

Applicant asserts that even if the teachings of Kuchler are relevant, the chart does not provide evidence that the cells of Huyghe et al. were infected after mid-log phase since the growth curve in Figure 3-1 shows the cells slightly before mid-log phase of growth.

A careful review of Figure 3-1 of Kuchler has been considered in view of applicant's remarks, but is found unpersuasive. If one were to draw a perfectly straight line parallel with the y-axis from the 60 hour point in Figure 3-1, the line would dissect the curve at exactly half-way, or mid-point, i.e. mid-phase. In addition, evidence that the cells of Huyghe et al. are infected

after mid-log phase is not necessary since the claims only require that the cells are infected between mid-log phase and stationary phase.

Applicant also states that the cells depicted in Figure 3-1 of Kuchler have a faster doubling time and would arrive at mid-log much faster than the 293 cells of the instant application. Applicant points to the declaration provided by Dr. Zhang as evidence that the doubling time of 293 cells is approximately 30 hours. Applicant assumes that if the doubling time of 293 cells is 30 hours, then the growth curve of Kuchler would be below mid-log.

Applicant's arguments as well as a review of the declaration have been fully considered, but are found unpersuasive. While the Quality Assurance Report states that the cell doubling time is approximately 30 hours, the Report does not indicate or imply which stage of log phase, i.e. early, mid or late log, the cells are in during this exponential growth phase. Therefore, from the evidence discussed in the previously, the rejection is maintained for reasons of record.

Claims 1, 3-9, 13-28, 30, 31, 38-49 and 51-62 are rejected under 35 U.S.C. 102(a) as being anticipated by Zhang et al. (WO 98/22588), as further evidenced by Wu et al. (US 6,689,600 B1) for reasons of record.

Claims 1, 3-9, 13-28, 30, 31, 38-49 and 51-62 are rejected under 35 U.S.C. 102(e) as being anticipated by Zhang et al. (US Patent No. 6,194,191 B1), as further evidenced by Wu et al. (US 6,689,600 B1) for reasons of record.

Applicant points to the declaration of Dr. Zhang and asserts that the instant invention was disclosed, but not claimed by the references cited. However, the entire disclosure of any reference disclosed to the public is available as prior art.

Applicant also states that Dr. Zhang indicates in the declaration that the process was invented by him and the other co-inventors listed in the present application.

A review of the inventorship of both the instant application and the Zhang et al. references has been reviewed. It is determined that the inventive entity of both Zhang et al. references and the instant application are different since Shawn Gallagher is not listed as an inventor for either WO 98/22588 or US 6,194,191 B1. Since the statutes under 35 USC § 102 (a) and (e) require a description or disclosure by another and the Zhang et al. references and the instant invention have different inventive entities, it is maintained that both Zhang et al. references constitute prior art against the instant claims.

Applicant further asserts that Wu et al. is not available as prior art. It is not clear what applicant intends by "what one of ordinary skill in the art understood from the Zhang reference because the inventors on the Wu reference are the inventors of the Zhang reference."

Contrary to applicant's assertion, Wu et al. is available as prior art. The benefit of priority to the instant application is December 1, 1998 and the priority date granted to Wu et al. extends to a provisional application that was filed on November 16, 1998. In any case, the evidentiary teaching provided by Wu et al. is not required to antedate the instant filing date because it is discloses evidence showing that the characteristic of when the cells of the Zhang et al. references are infected is at mid-log. See MPEP §§ 2131.01 and 2124.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 10-12 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huyghe et al. as applied to claims 1, 3, 8, 9, 13-25, 31, 38, 47, 49 and 51-62 above **or** Zhang et al. (WO 98/22588) **or** Zhang et al. US (6,194,191) as applied to claims 1, 3-9, 13-28, 30, 31, 38-49 and 51-62.

Applicant asserts that there is a contradiction between the seeding density being a crucial component of the log phase in the rejection of Huyghe et al. and that the instant seeding densities are merely a subjective determination.

In response, there is no discrepancy between the discussions. The seeding density is crucial for the log phase. Freshney, supplied to the Office by applicant, teaches this fact. It is also established by the teachings of the Kuchler that Huyghe et al. infect the cells at mid-log phase. Huyghe et al. do not disclose subjective factors, such as the condition of the cells before plating or the nature of the cell divisions, ect., but since the cells are required by the reference to be "about 50-60%" confluent at the time of infection, the exact number of cells plated by Huyghe et al. would have been a critical element in order to reach the required log phase by 60 hours.

Applicant also asserts that Huyghe et al. does not stand for reasons discussed previously. However, the reasons presented by applicant against Huyghe et al. are found to be insufficient.

Applicant also states that the Office has not explained how Huyghe et al. teach or suggest the adenovirus formulations of claim 29. Huyghe et al. teach a method of improving the quantity and/or purity of the recombinant virus obtained. Therefore, it would have been prima facie

obvious to one of ordinary skill to test any one of the properties listed to ensure a good yield of adenovirus.

Applicant maintains that Zhang et al. is not prior art. However, this assertion is rendered moot since each Zhang et al. reference is a different inventive entity from the instant application.

Claims 2 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huyghe et al. as applied to claims 1, 3, 8, 9-12, 13-25, 29, 31, 38, 47, 49 and 51-62 above **or** Zhang et al. (WO 98/22588) **or** Zhang et al. US (6,194,191) as applied to claims 1, 3-31, 38-49 and 51-62 and further in view of Graham et al. (C31 of IDS) and Leu et al. (6,194,210 B1) for reasons of record.

Applicant argues that the statement by the Office that the teachings of Leu et al. are applicable to the general viral propagation art does not make it so. Applicant asserts that the discussion about other viruses in Leu et al. is referring to viruses that can be propagated in hosts, not that they can infect cells at late-log phase. Applicant also argues that it has not been explained how Leu et al. can be combined with Huyghe et al., i.e. whether infecting cells at different phases of growth are beneficial to achieve increased production of adenovirus. Applicant also agues that there does not appear to be a reason why the skilled artisan would turn to the teachings of Leu et al. Applicant cites case law for support.

In response, the Office does not make the statement about Leu et al. without explicit support from the reference, see column 5, lines 29-32, column 11, lines 18-column 12, line 9 and claims 1 and 4. The list of various viruses discussed by Leu et al. apply to the method of producing large quantities of virus, see claims 1 and 4. Making large quantities of virus, explicitly claimed by Leu et al., would have been the motivating factor for one of ordinary skill

in the art to modify the teachings of Huyghe et al. by infecting cells at late-log phase, see column 11, lines 18-column 12. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art (emphasis added). See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation of producing large quantities of virus is found explicitly within the teaching of Leu et al. Leu et al. accomplish this by infecting cells in late-log phase. One of ordinary skill in the art at the time the invention was made would have been had a reasonable expectation of growing the adenovirus of Huyghe et al. or either Zhang et al. reference with the cell culture method steps taught by Leu et al. because Leu et al. teach that a wide range of viruses may be propagated to generate vaccines using the method steps, see column 5, lines 29-32 and Graham et al. teach infecting cells at 80-90% (late-log phase) with adenovirus, see section 3.1.2 on page 117. Therefore, Graham et al. clearly demonstrate that the teachings of Leu et al. are applicable to adenovirus infection in cells at late-log phase of growth. Therefore, the rejections are maintained for reasons of record.

With respect to Leu et al. and Graham et al. in view of either Zhang et al. reference, applicant cites the declaration of Dr. Zhang. However, since this declaration does not obviate the primary rejections of record for reasons discussed above.

Claims 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huyghe et al. as applied to claims 1, 3, 8, 9-12, 13-25, 29, 31, 38, 47, 49 and 51-62 above, and further in view of Graham et al. (C7) for reasons of record.

Applicant argues that Graham et al. do not cure the deficiencies of Leu et al., Huyghe et al. or either Zhang et al. reference. Applicant also argues that Graham et al. do not provide a motivation to combine Leu et al., Huyghe et al. or either Zhang et al. reference.

Applicant's arguments have been fully considered, but are found unpersuasive since there are no deficiencies for Graham et al. to cure. Motivation(s) for combining Huyghe et al. or either Zhang et al. reference with Leu et al. are supplied in the previous rejection.

Claims 4, 30, 39-46 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huyghe et al. as applied to claims 1, 3, 8, 9-12, 13-25, 29, 31, 38, 47, 49 and 51-62 above, and further in view of Garnier et al. (C26) and Spier et al. (C35 of the IDS) for reasons of record.

Applicant maintains that the 293 cells of Huyghe et al. are infected at early log phase. However, this assertion remains unsupported.

Applicant also states that Garnier et al. is only concerned with an increase in the production of heterologous proteins and not adenovirus titers. Applicant also states that the rejection is silent with respect to when infection of the cells took place. Applicant concludes that Spier et al. do not even mention adenovirus and therefore, does not provide a motivation for the combination of references cited.

Applicant's arguments as well as a review of the reference have been fully considered, but are found unpersuasive. The scale-up method "to improve the volumetric yield of the [adenovirus] recombinant protein production system" quoted by applicant necessarily requires an increased yield of adenoviruses carrying the heterologous protein. An increase of protein produced/or expressed by the adenovirus necessarily means that more adenovirus is present in greater quantities, i.e. a volumetric yield. The teachings of Garnier et al. are not required to

teach when infection took place because this teaching is supplied by Huyghe et al. It is established that Huyghe et al. teach infection at the mid-log phase. Spier et al. review conventional techniques used in the virus propagation art. One of ordinary skill would have been motivated to use a conventionally applied culture system, described by Spier et al. in the method and system of Huyghe et al. and Garnier et al. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in using any of the culture systems of Spier et al. in the method of Garnier et al. and Huyghe et al. because Garnier et al. use a bioreactor system to propagate large quantities of adenovirus and Spier et al. review various types of bioreactor systems.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art, absent unexpected results to the contrary.

Conclusion

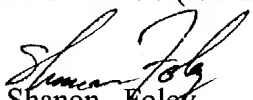
THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (571) 272-0898. The examiner can normally be reached on M-F 10:00 AM - 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Shanon Foley
Primary Examiner
Art Unit 1648